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Environmental enrichment preserved lifelong ocular dominance plasticity, but did not improve visual abilities

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ABSTRACT

In standard cage (SC)-raised mice, ocular dominance (OD) plasticity of the primary visual cortex (V1) induced by monocular deprivation (MD) is maximal in juveniles, declines in adults, and is absent beyond postnatal day (PD) 110. Raising mice in an enriched environment (EE) preserved a juvenile-like OD plasticity after 7 days of MD until at least PD196, mediated by reductions of deprived eye responses in V1. Whether the sensitive phase for OD plasticity can be prolonged into older age and whether long-term EE modifies visual abilities was not yet known. Here, we demonstrate that EE raising enables lifelong OD plasticity. In contrast to PD200 EE-mice, the preserved OD shift in both >PD400 and >PD700 EE-mice was mediated by increases in open eye responses in V1 (adult OD plasticity). When SC-mice were transferred to EE after PD110, OD plasticity was restored until PD922. Moreover, visual abilities tested by both optomotry and the visual water task and interindividual variability were not different between PD700 SC- and EE-mice. Taken together, EE raising enabled a lifelong OD plasticity but did not affect basic visual performance.

1. Introduction

Neuronal plasticity describes the ability of the brain to modify its circuitry in response to changing behaviors and environments. This ability to adapt is especially crucial for learning, memory, and recovery from brain injuries. Early in life, neuronal plasticity is high but declines during aging. A well-studied model to investigate cortical plasticity is ocular dominance (OD) plasticity in the visual cortex induced by depriving one eye of vision. Neurons in the binocular part of primary visual cortex (V1) receive inputs from both eyes but are dominated by the contralateral eye. Depriving V1 of input from one of the eyes by monocular deprivation (MD) causes a shift in the OD toward the open eye (Dräger, 1978; Wiesel and Hubel, 1963). This kind of plasticity is age dependent in mice raised in standard cages (SCs; Espinosa and Stryker, 2012): during the critical period of mice (PD19–32), 4 days of MD are sufficient to induce an OD shift toward the open eye (Gordon and Stryker, 1996). This juvenile OD shift is predominantly mediated by a decrease in the cortical responses to visual stimulation of the deprived eye. In contrast, in 2–3 month-old SC-raised mice, significant OD shifts need 7 days of MD and are primarily mediated by increased open eye responses in V1 (adult OD plasticity), while reductions of deprived eye responses are no longer observed (Heimel et al., 2007; Hofer et al., 2006; Sato and Stryker, 2008; Sawtell et al., 2003). Using optical imaging of intrinsic signals, OD plasticity after 7 days of MD is absent in SC-mice beyond PD110 (Lehmann and Löwel, 2008).

In contrast to SCs, an enriched environment (EE) provides increased physical (running wheels), social (bigger housing groups), and cognitive (regularly changed labyrinths or toys) stimulation (Rosenzweig et al., 1962). Housing rodents in EE cages has been shown to enhance plasticity of the visual cortex (Baroncelli et al., 2010, 2012; Sale et al., 2007b; Scali et al., 2012), to speed up visual system development (Cancedda et al., 2004; Landi et al., 2007b; Sale et al., 2007a) and elicit remarkable changes in the brain, ranging from molecular to anatomic and functional levels [for a review see Sale et al. (2014)]: increased levels of brain-derived neurotrophic factor (Cancedda et al., 2004; Falkenberg et al., 1992; Ickes et al., 2000; Sale et al., 2004), serotonin (Baroncelli et al., 2010) and insulin-like growth factor I (Sale et al., 2007a) reduced extracellular GABA (Baroncelli et al., 2010; Sale et al., 2007b) and local inhibition in V1 (Greifzu et al., 2014). EE raising

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is also able to restore already lost plasticity in rats (Baroncelli et al., 2010, 2012; Sale et al., 2007b) and mice (Greifzu et al., 2014).

When we raised C57BL/6J mice in an EE, OD plasticity after 7 days of MD was not only preserved up to PD196 (oldest animal tested) but also OD shifts in these EE-mice were mediated by reductions in deprived eye responses in V1. These reductions are a hallmark of juvenile OD plasticity, and in SC-mice not observed beyond the critical period. Thus, adult (PD200) enriched mice displayed juvenile-like OD plasticity (Greifzu et al., 2014).

Whether the sensitive phase for OD plasticity can be prolonged into even older age and whether long-term EE modifies visual abilities was not yet known. We, therefore, raised mice in EE cages until they were beyond 2 year old and then tested for OD plasticity with intrinsic signal optical imaging (Kalatsky and Stryker, 2003). We observed that OD plasticity was present lifelong in EE-mice, both in animals raised in EE from birth as well as in mice transferred from SCs to EE at PD110. The oldest mouse in our study was already 922 days old and still displayed an OD shift. Notably, the observed adult OD shifts in the old EE-mice (PD402-PD809) were mediated by increases in open eye responses in V1.

There is also a debate in the field whether enriched raising conditions affect sensory performance and interindividual variability (Bayne and Würbel, 2014). We, therefore, used 2 different vision tests in both SC- and EE-mice of about PD700. First, the visual water task, a cortex-dependent visual discrimination paradigm, to measure visual acuity and orientation discrimination (Prusky et al., 2000b). Second, the virtual-reality optomotry setup (Prusky et al., 2004) to measure the spatial frequency threshold ("visual acuity") and the contrast threshold ("contrast sensitivity") of the optomotor reflex and its experience-induced changes after MD (Prusky et al., 2006). We did neither find evidence for increased visual abilities of enriched mice nor for an increased interindividual variability. Taken together, EE preserved lifelong OD plasticity in mouse V1 but did not affect basic visual abilities.

2. Materials and methods

2.1. Animals

C57BL/6J mice were obtained from the mouse colony of the central animal facility of the University Medical Center, Göttingen, Germany, and housed in an animal room with a 12-h light/dark cycle, with food and water available ad libitum. All experimental procedures were approved by the local government: Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit.

We used both male and female mice for our study. In the EE >PD400 group, male mice with an age range of PD400–487 were used. The EE >PD700 mice were females and PD730-816. The "late EE-mice" (mice transferred from SC to EE cages at PD110, details in the following) were females and PD847–922. All mice that were analyzed with optical imaging were measured in the optomotor setup before. For the visual water task measurements, we used male SC-mice (PD690) and female EE-mice (PD687). We had to use female mice for the oldest EE groups because male mice in the EE cages tend to fight a lot, especially when they grow older. Moreover, for the late EE group, we had to transfer mice from different SCs to EE to obtain a sufficiently large number of animals for the social enrichment. Because adult male mice from different cages would seriously fight if put together, we had to use female mice for that group. We had already addressed the issue of different sexes in a previous study and observed that the prolonged sensitive phase for OD plasticity in the EE-mice was due to the EE rearing and not caused by a sex difference of the experimental animals (Greifzu et al., 2014).

2.2. Housing conditions

2.2.1. Standard cages

Our SCs were 26 × 20 × 14 cm large, and we housed 3–5 animals of the same litter and sex together. The cages were translucent with an open grid cover and wood chip bedding.

2.2.2. Enriched environment

To raise EE-mice, pregnant dams were put into commercially available EE cages (Marlau; Fares et al., 2012; Greifzu et al., 2014) about 1 week (3–7 days) before delivery. Females and males were separated at PD30. Mice were housed in groups of 9–15 animals. For the late EE paradigm, mice were raised in an SC and transferred to EE at PD110. The EE cages (56 × 37 × 32 cm) are about 9 times larger than our SCs, with 2 floors linked by a ladder for going up and a tube for sliding down. They are equipped with 3 running wheels and a red tunnel to protect the animals from light. The mice had to pass through the maze in the upper compartment to get both food and water positioned in the lower compartment. The maze was changed 3 times a week, and there were in total 12 different configurations.

2.3. Monocular deprivation

The right eye was deprived for 7 days according to published protocols (Cang et al., 2005; Gordon and Stryker, 1996; Lehmann and Löwel, 2008). Animals were checked daily to make sure that the eyes remained closed.

2.4. Visual water task

To measure perceptual thresholds, we used the visual water task, a visual discrimination task based on reinforcement learning (Prusky and Douglas, 2004; Prusky et al., 2000b).

For measuring visual acuity, animals are initially trained to distinguish a low spatial frequency grating (0.086 cyc/deg) from equiluminant gray and then their ability to recognize higher spatial frequencies is tested. The apparatus consists of a trapezoidal-shaped pool with 2 monitors placed side by side at one end. A midline divider is extended from the wide end into the pool, creating a maze with a stem and 2 arms. An escape platform that is invisible to the animals is placed below the monitor, where the grating is projected. The position of the grating and the platform is alternated in a pseudorandom sequence over the training and test trials. When 90% accuracy is achieved 3 times (training phase), the testing phase starts: an individual's visual acuity threshold is determined by increasing the spatial frequency of the grating until performance falls below 70% accuracy. The highest spatial frequency at which 70% accuracy is achieved is taken as the maximum visual acuity. To measure visual acuity, both SC- (PD690) and EE-raised mice (PD689, at last day of measurements) were trained and tested in the visual water task.

As a second parameter, we determined the animals' orientation discrimination, using the visual water task. To this end, mice were trained to distinguish between horizontal and vertical square wave gratings of a low spatial frequency (0.086 cyc/deg, training phase). Once 90% accuracy was achieved, the test phase was started. To test the orientation discrimination ability of each mouse, the orientation difference of the 2 gratings was reduced stepwise by 5° until performance fell below 70% accuracy. The smallest orientation difference at which 70% accuracy was achieved was taken as the minimum orientation discrimination.

2.5. Virtual-reality optomotor setup

Both the spatial frequency and the contrast thresholds of the optomotor reflex of all mice (animals with and without MD) were

measured using the optomotor system (Prusky et al., 2004). First, a baseline measurement was performed, then some animals received an MD, and measurements were continued daily for the following 7 days.

2.6. Optical imaging of intrinsic signals

After completion of all behavioral vision tests, visual cortical responses were recorded and analyzed as described previously (Greifzu et al., 2011, 2014).

2.6.1. Surgery

Briefly, mice were box-anesthetized with 2% halothane in O_2:N_2O (1:1) and injected with atropine (0.1 mg/mouse s.c.; Franz Köhler), dexamethasone (0.2 mg/mouse s.c.; Ratiopharm), and chlorprothixene (0.2 mg/mouse i.m.; Sigma). After placing animals in a stereotaxic frame, anesthesia was maintained with 0.8% halothane in a 1:1 mixture of O_2:N_2O.

2.6.2. Data acquisition and visual stimulation

Mouse V1-responses were recorded through the skull using the "Fourier"-imaging method of Kalatsky and Stryker (2003) and optimized for the assessment of OD plasticity (Cang et al., 2005). V1-signals were visualized with a CCD-camera (Dalsa 1M30) using a 135 × 50 mm tandem lens configuration (Nikon), with red illumination light (610 ± 10 nm). Active brain regions absorb more of the red light and appear darker in the images. Frames were acquired at a rate of 30 Hz, temporally binned to 7.5 Hz, and stored as 512 × 512 pixel images after spatial binning of the camera image.

Visual stimuli were presented on a high refresh rate monitor (Hitachi, ACCUVUE, HM-4921-D, 21″) positioned 25 cm from the eyes. Stimuli consisted of drifting white horizontal bars (2° wide; −5 to +15° of the visual field) as described previously (Greifzu et al., 2014). The amplitude component of the optical signal represents the intensity of neuronal activation (expressed as fractional change in reflectance $\times 10^{-4}$) and was used to calculate OD. At least 2–3 maps per animal were averaged to compute the ocular dominance index (ODI) as follows: (C − I)/(C + I), with C and I representing the response magnitudes of each pixel to visual stimulation of the contralateral and ipsilateral eye. The ODI ranges from −1 to +1, with negative values representing ipsilateral and positive values representing contralateral dominance.

2.7. Statistical analyses

All intragroup and intergroup comparisons were analyzed by a two-tailed Student *t*-test and Bonferroni correction where indicated. The intergroup comparison of the enhancement of visual acuity was analyzed by analysis of variance (ANOVA) with repeated measurements. F-test was used to test differences in variance. The levels of significance were set as $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. Data are represented as means ± standard error of the mean.

3. Results

3.1. Environmental enrichment extended OD plasticity into old age

In EE-mice without MD, V1-activation in the binocular zone was dominated by the contralateral eye. Because more active brain regions absorb more of the red light with which the cortex was illuminated, activity patches induced by visual stimulation of the contralateral eye appear darker than those after ipsilateral eye stimulation (Fig. 1A). To quantify the relative strength of V1-activation after left and right eye stimulation, we computed an ODI, and this index is color-coded in the two-dimensional OD map, with warm colors indicating contralateral and cold colors ipsilateral dominance. In non-deprived V1, OD maps displayed warm colors, the histogram of all ODIs was centered to the right of 0, and the average ODI was positive (Figs. 1A and 2A). Seven days of MD in EE-raised mice above PD400 (group name: >PD400) induced an OD shift toward the open eye (Fig. 1B and C): the activity patch induced by stimulation of the open (ipsilateral) eye was as dark as the patch induced by stimulation of the deprived (contralateral) eye, colder colors predominated the OD map, and the ODI histogram was shifted to the left. Quantitative analyses of V1-activation showed that the ODI decreased from 0.25 ± 0.02 without MD (n = 5; age range: PD422–429) to 0.07 ± 0.03 after MD in old EE-mice of the >PD400 group (age range: PD402–487; n = 6; $p = 0.002$, *t*-test; Fig. 2A). To test whether EE housing can expand the sensitive phase for OD plasticity even further, we additionally imaged visual cortical responses in over 23-month-old EE-mice (group name: >PD700, age range: PD730–809). Again, 7 days of MD induced strong OD plasticity: activity patches in V1 were equally dark after stimulation of the open and deprived eye, OD maps were dominated by colder colors and the ODI histogram shifted to the left (Fig. 1C). The ODI after MD was 0.01 ± 0.04 (n = 5; $p = 0.001$, *t*-test, compared to >PD400 no-MD; Fig. 2A).

The OD shifts of the old EE-mice (>PD400 and >PD700) were primarily mediated via increases in open eye responses in V1. In the >PD400 group, V1-activation via the open (ipsilateral) eye increased from 0.99 ± 0.06 in mice without MD to 1.43 ± 0.16 after MD ($p = 0.039$, *t*-test; Fig. 2B). In contrast, deprived (contralateral) eye responses in V1 did not change (without/with MD: 1.54 ± 6.06/1.53 ± 0.12; $p = 0.910$, *t*-test). In the >PD700 group, V1-activation via the contralateral or ipsilateral eye after MD was again similar (contra/ipsi: 1.31 ± 0.13/1.32 ± 0.10; $p = 0.97$, *t*-test): ipsilateral eye responses in V1 were higher than in the non-deprived >PD400 group ($p = 0.028$, *t*-test), whereas contralateral eye responses were not different (n = 5; $p = 0.169$, *t*-test), indicating that OD plasticity was most likely again mediated by increases of open eye responses in V1 (Fig. 2B).

3.2. EE restored OD plasticity into old age

We already showed that OD plasticity can be restored in SC-raised mice by EE housing (starting at PD110) up to an age of at least PD320 [oldest mouse tested; Greifzu et al., (2014)]: After 7 days of MD, the ODI of late EE-mice with an average age of PD250 was 0.07 ± 0.04 (n = 5; age range: PD212–320) and, thus, significantly lower than the 0.25 ± 0.02 of animals without MD (n = 6; $p = 0.008$, *t*-test; age range: PD222–344; Fig. 2C). However, it was not yet clear whether the re-induced plasticity would persist into older age. To this end, we transferred another group of mice from SC into EE at PD110 ("late EE") and imaged V1-activities after PD730. Owing to the rather advanced age of these animals, we decided to perform only experiments with 7 days of MD (and no controls without MD) to reach a maximal number of mice. Fortunately, we managed to record V1-activity maps of sufficient quality in 2 old mice aged PD851 and PD922 (group name >PD800). In both late EE-mice, OD plasticity was still present: After MD, activity patches in V1 were equally dark after stimulation of the deprived and open eye, OD maps were dominated by colder colors and the ODI histogram was centered around 0 (Fig. 1D). The average ODI was 0.02 ± 0.06 (n = 2; >PD800; Fig. 2C), and the activity values in V1 after contralateral and ipsilateral eye stimulation were rather similar (contra/ipsi: 1.67 ± 3.31/1.85 ± 0.52; n = 2; Fig. 2D). Thus, mice display OD plasticity after MD until an age of at least 2.5 years, if housed in an EE from at least PD110.

3.3. Basic visual abilities and enhanced optomotor reflex after MD were similar in old SC- and EE-mice

We measured the visual abilities of both SC-mice (PD690) and EE-mice (PD400–922) in 2 different behavioral vision tests: the

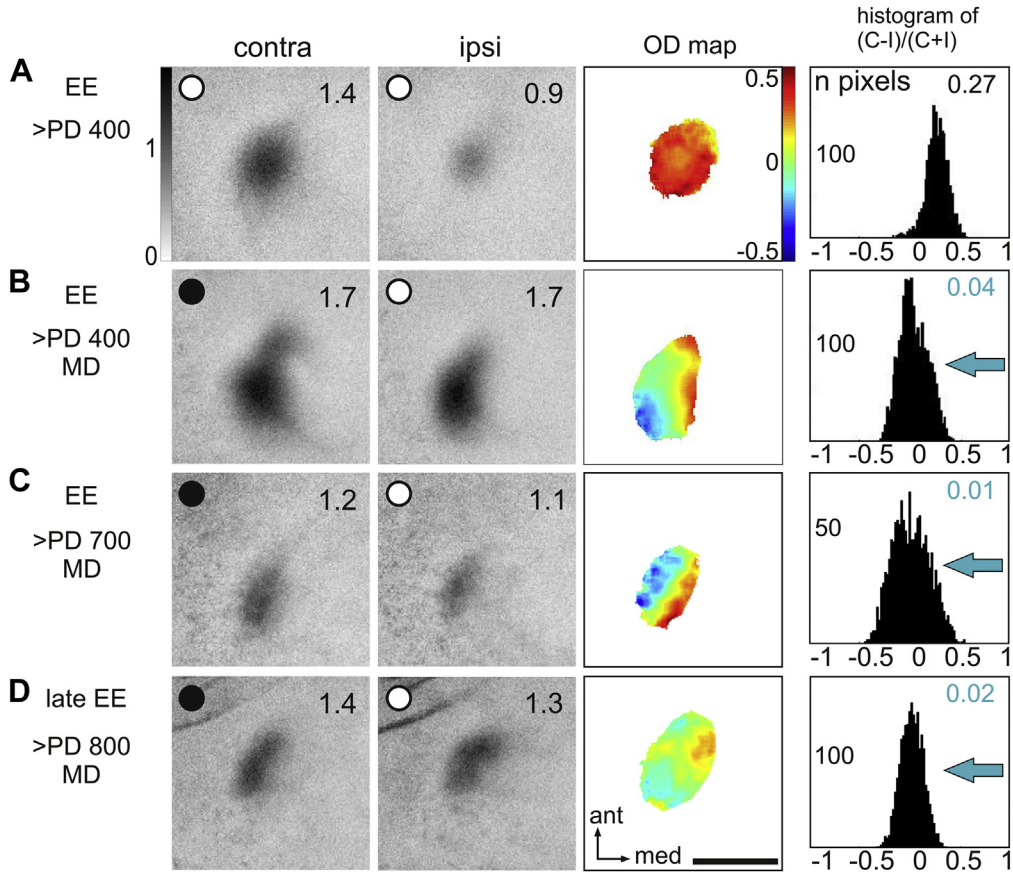

Fig. 1. Environmental enrichment preserved lifelong ocular dominance plasticity in mouse primary visual cortex (V1). Optically recorded activity maps of the contralateral (contra) or ipsilateral (ipsi) eye in binocular V1 of old mice raised in EE (A–C) or transferred from a SC to EE at postnatal day 110 (late EE, [D]) before (A) and after 7 days of monocular deprivation (B–D). Grayscale-coded response magnitude maps (numbers correspond to quantified V1-activation), 2-dimensional OD maps, and the histogram of OD scores, including the average ODI, are illustrated. MD eye is indicated by a (black) filled circle. (A) In EE-mice older than PD400 (>PD400; illustrated example: PD425) without MD, activity patches evoked by stimulation of the contralateral eye were darker than those of the ipsilateral eye, the average ODI was positive, and warm colors prevailed in the OD maps, indicating contralateral dominance. (B and C) After 7 days of MD, there was a strong OD shift toward the open eye in both EE-mice older than PD400 (B) (>PD400; illustrated example: PD432) and older than PD700 (C) (>PD700; illustrated example: PD808): after MD, the contralateral and ipsilateral eye activated V1 with nearly equal strength, colder colors prevailed in the OD map, the histogram of OD scores shifted to the left (blue arrow), and the average ODI was lower. (D) Even late EE-mice that were transferred to EE only after PD110 continued to display OD plasticity into old age (>PD800). The mouse of the illustrated V1 was already 922-days old and still showed an OD shift of a magnitude seen in 4-week-old standard cage raised mice. Scale bar: 1 mm. Abbreviations: EE, enriched environment; OD, ocular dominance; ODI, ocular dominance index; MD, monocular deprivation; PD, postnatal day. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

visual water task, a cortex-dependent paradigm of visual discrimination learning (Prusky et al., 2000b), and the virtual-reality optomotor setup (Prusky et al., 2004), measuring the spatial frequency and contrast threshold of the optomotor reflex which is mediated by subcortical circuitry. In both tests, visual performance and variation of values were indistinguishable between old SC- and EE-mice as was the learning speed for the visual water task.

3.3.1. Visual water task: visual acuity, orientation discrimination, and learning the visual water task were similar in EE- and SC-raised mice

3.3.1.1. Visual acuity. Old SC-mice (PD690) had a visual acuity of 0.51 ± 0.02 cyc/deg (n = 4), very similar to the 0.48 ± 0.01 cyc/deg (n = 4) of old EE-mice (PD687). Values and variance were not different between SC- and EE-mice ($p = 0.325$, *t*-test; $p = 0.470$, F-test Fig. 3A).

3.3.1.2. Orientation discrimination. To test visual abilities of the same mice in a more elaborate perceptual task, we measured orientation discrimination, again using the visual water task (Pielecka-Fortuna et al., 2014). To perform the task, the mice first had to learn to swim toward the rewarded grating under which the escape platform was located. There was no difference in the learning curves of animals between the 2 housing conditions: SC- and EE-raised mice completed the training phase with 19.2 ± 3.3 (n = 5) and 14.4 ± 1.2 (n = 5; $p = 0.210$, *t*-test) training blocks, corresponding to 6.5 and 5 days, respectively. The variance of SC and EE-mice values was not different ($p = 0.077$, F-test).

Next, the orientation discrimination threshold of individual animals was identified by gradually decreasing the orientation difference of the rewarded and a distractor grating. SC-mice needed at least an orientation difference of 23.7 ± 4.4° (n = 5) for a correct behavioral choice, EE-mice needed 17.9 ± 2.5° orientation difference (n = 5; Fig. 3B). Orientation discrimination was not different between the groups ($p = 0.286$, *t*-test), neither was the variance ($p = 0.293$, F-test).

3.3.2. Virtual-reality optomotor setup: similar spatial frequency and contrast thresholds of the optomotor reflex in EE- and SC-mice

3.3.2.1. Spatial frequency threshold. In SC-mice, the spatial frequency threshold of the optomotor reflex was 0.36 ± 0.002 cyc/deg (PD690; n = 5), not different compared with 0.36 ± 0.004 cyc/deg in EE-mice (PD687; n = 4; $p = 0.735$, *t*-test; Fig. 3C). Moreover, the variance of the values of the 2 groups was not different ($p = 0.272$,

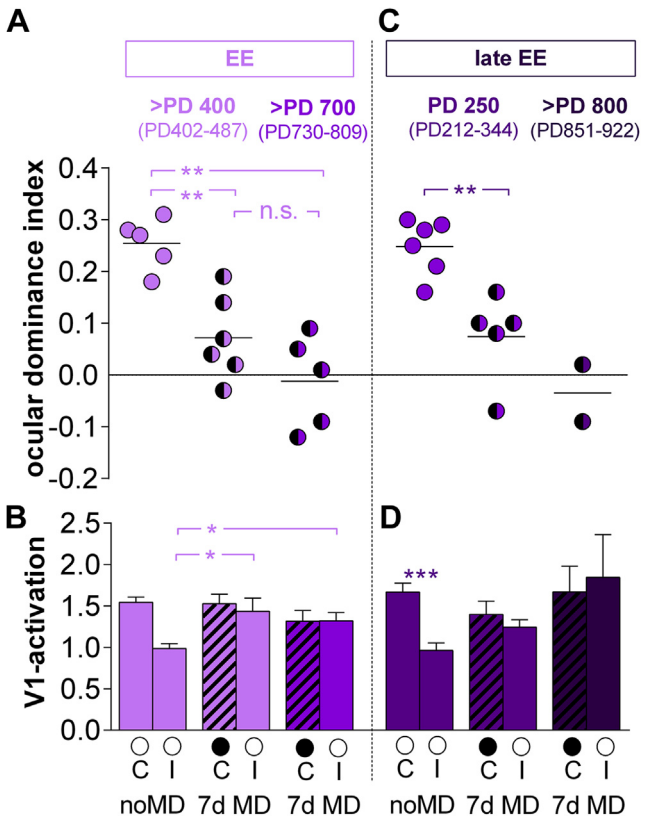

Fig. 2. Quantification of V1-activation in old EE and late EE-mice. (A and C) Optically imaged OD indices in mice raised in EE (A) or transferred from standard cages (SCs) to EE at PD110 (late EE) (C). Symbols represent ODI values of individuals; means are marked by horizontal lines. (B and D) V1-activation elicited by stimulation of the contralateral (C) or ipsilateral (I) eye in control animals and after MD (black filled circle indicates MD eye). PD250 late EE-mice are from Greifzu et al. (2014). Note that the OD shift in EE-mice is mediated by an increase in open eye responses in V1. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Abbreviations: EE, enriched environment; MD, monocular deprivation; OD, ocular dominance; ODI, ocular dominance index; PD, postnatal day.

F-test). As expected (Douglas et al., 2005), spatial frequency thresholds of the optomotor reflex of both SC- and EE-mice revealed lower values compared with the measurements of the perceptual visual acuity threshold measured in the visual water task (SC: $p = 0.003$, EE: $p = 0.0004$, t-test).

3.3.2.2. Contrast sensitivity. Contrast sensitivity thresholds were measured at 6 different spatial frequencies in 3 groups of old EE-mice: >PD400 EE-mice (age range: PD400–487; n = 12), >PD700 EE-mice (age range: PD730–816; n = 8), and >PD800 late EE-mice (age range: PD847–922; n = 3). Values of >PD400 EE-/>PD700 EE-/>PD800 late EE-mice were 3.5 ± 0.1/3.7 ± 0.05/4.0 ± 0.1 (corresponding to 28/27/25% contrast) at 0.031 cyc/deg, 12.3 ± 1.6/8.9 ± 0.2/12.0 ± 1.3 (8/11/8% contrast) at 0.064 cyc/deg, 11.0 ± 1.3/8.2 ± 0.2/10.7 ± 1.1 (9/12/9% contrast) at 0.092 cyc/deg, 10.2 ± 1.3/7.7 ± 0.2/10.3 ± 1.2 (10/13/10% contrast) at 0.103 cyc/deg, 6.2 ± 0.5/6.8 ± 0.2/8.0 ± 0.5 (16/15/13% contrast) at 0.192 cyc/deg, and 3.4 ± 0.2/3.6 ± 0.1/3.9 ± 0.1 (30/28/26% contrast) at 0.272 cyc/deg ($p >$ 0.05 for all measured spatial frequencies and comparisons between all groups, t-test, Bonferroni adjusted).

3.3.3. Similar experience-enabled improvement of the optomotor reflex of the open eye after MD

Both the spatial frequency and the contrast thresholds of the optomotor reflex of the open eye typically improve after MD (Prusky et al., 2006). Because this experience-enabled visual improvement declines with age in SC-mice (Lehmann et al., 2012), we wondered whether EE raising might prevent this age-dependent decline in optomotor improvement. To this end, we measured both the spatial frequency and the contrast sensitivity thresholds of the optomotor reflex of the open eye of all EE-mice during the 7-day MD period (before the optical imaging experiments; Fig. 4).

3.3.3.1. Experience-enabled improvements in spatial frequency thresholds. Values of the 2 EE groups (>PD400, >PD700) and the late EE group (>PD800) after MD are displayed in Fig. 4A, average gain on baseline in Fig. 4B. Traces of individual mice from the EE groups are displayed in Fig. 4C–H. After 7 days of MD and daily testing, spatial frequency thresholds of the open eye improved in EE-raised mice of both age groups (Fig. 4A and B). In >PD400 mice, they improved by 20 ± 1% from 0.37 ± 0.002 before MD to 0.45 ± 0.007 cyc/deg after MD (n = 7; PD400–487; $p = 0.0001$, t-test; Fig. 4A, C, D). This increase was different from age-matched EE-mice without MD in which values did not change during the 7-day measuring period (no MD; day 0/7: 0.35 ± 0.01/0.37 ± 0.001 cyc/deg; n = 5; PD422–429; $p = 0.221$, t-test; compared with MD group: $p = 0.000$, $F_{1,10} = 35.709$, ANOVA).

In EE-raised mice >PD700, spatial frequency thresholds improved by 21 ± 4% from 0.31 ± 0.01 to 0.37 ± 0.01 cyc/deg after

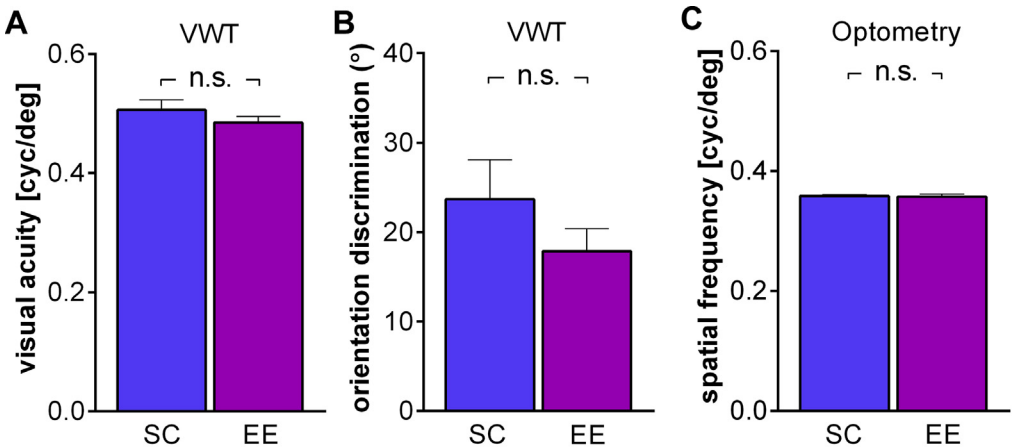

Fig. 3. Basic visual performance of old SC- and EE-mice was similar. Visual abilities of SC- (PD690) and EE-mice (PD687) were tested with the visual water task ([A] and [B]) and the optomotry system (C) (measuring the threshold of the optomotor reflex). Visual acuity (A), orientation discrimination (B) and spatial frequency threshold (C) of mice of both rearing groups were indistinguishable. Abbreviations: EE, enriched environment; n.s., not significant; SC, standard cages; VWT, visual water task.

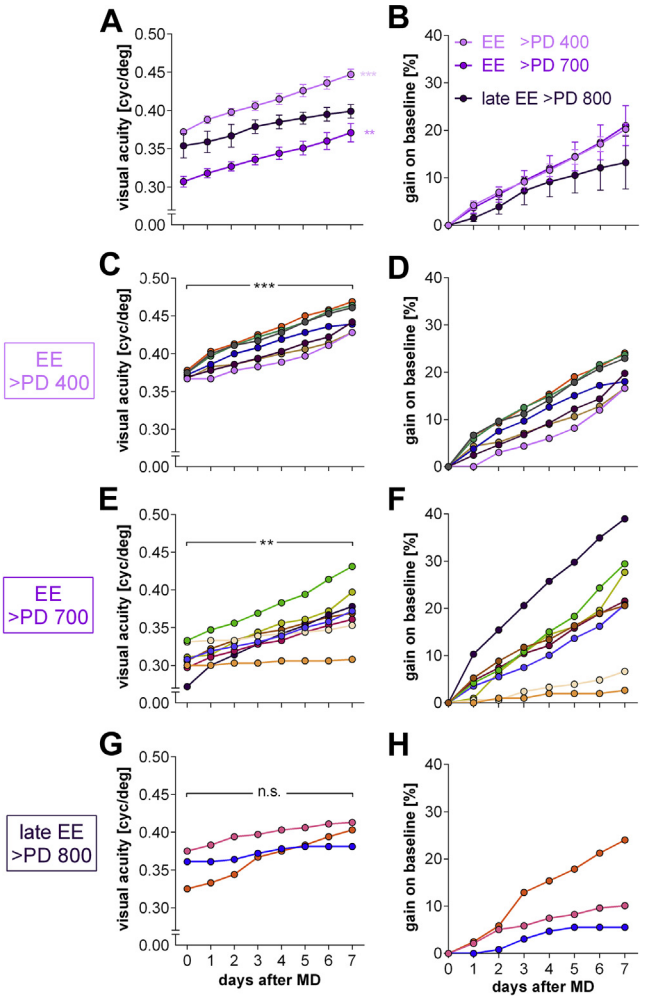

Fig. 4. Enhanced optomotor reflex after MD in old EE and late EE-mice. The spatial frequency threshold ("visual acuity") of the optomotor reflex of the open eye was tested daily after MD. Visual acuity (A, C, E, G) in cycles per degree (= cyc/deg) and gain on baseline in % (B, D, F, H) are plotted as a function of days after MD. Mean values of the 3 EE groups (EE >PD400, EE >PD700, late EE >PD800) (A and B) as well as the values of individual mice are illustrated (C–H). Note that there was a pronounced increase in interindividual variability in the EE-mice with age (compare [C] with [E] and [D] with [F]). $^{**}p < 0.01$, $^{***}p < 0.001$. Abbreviations: EE, enriched environment; MD, monocular deprivation; PD, postnatal day.

7 days of MD (n = 8; PD730–816; $p = 0.001$, *t*-test; Fig. 4A, E, F). This increase was indistinguishable from >PD400 mice with MD ($p = 0.956$, $F_{1,13} = 0.003$, ANOVA; Fig. 4A). Note that the baseline visual acuity on day 0 (before MD) was significantly lower in the "older" EE-mice (>PD700) compared to the "younger" EE-mice (>PD400; $p < 0.0001$, *t*-test). Such an age-related decrease in basic visual abilities was described before for SC-mice (Lehmann et al., 2012). In late EE-mice >PD800, spatial frequency thresholds increased by 13 ± 6% from 0.35 ± 0.02 to 0.40 ± 0.01 cyc/deg after MD (n = 3; PD847–922; Fig. 4A, G, H). The increase was statistically not significant, most likely due to the limited number of the very old animals (>PD800; $p = 0.178$, *t*-test). Nevertheless, the increase of the values over the 7-day MD period was not different from the increase observed in >PD700 EE-mice which were housed in EE since birth ($p = 0.429$, $F_{1,9} = 0.685$, ANOVA). Moreover, the gain on baseline was also not different between the 3 EE groups ($p > 0.05$ for all comparisons, *t*-test; Fig. 4B).

Concluding, there was no obvious age-dependent decrease of the experience-enabled visual improvements of the optomotor reflex of the open eye after MD between the >PD400 and >PD700 EE group. This is in contrast to SC-mice, in which such a difference was described between 7- and 23-month-old animals (Lehmann et al., 2012). However, the age-dependent increase in interindividual variability was similar between the 2 old EE groups (>PD400 and >PD700; Fig. 4C–F) and also similar to the one described before for old SC-mice of approximately the same age (Lehmann et al., 2012): for example, the standard deviation of the gain on baseline values on day 7 after MD was 12% in >PD700 mice and, thus, significantly higher than the 3% of the "younger" >PD400 group ($p = 0.006$, F-test; Fig. 4D, F). The variance of our >PD700 mice was comparable with the age-matched 23-month-old SC-mice described previously (Lehmann et al., 2012; $p = 0.433$, F-test).

3.3.3.2. Experience-enabled improvement in contrast sensitivity thresholds. The experience-enabled improvements of the contrast sensitivity thresholds of the optomotor reflex of the open eye after MD were essentially similar to the results for the spatial frequency thresholds, measured in the same mice. The contrast sensitivity thresholds improved at all spatial frequencies, that is, the optomotor reflex was already triggered by gratings of lower contrast. Table 1 lists values of all groups at all measured spatial frequencies. As an example, values from 0.064 cyc/deg are described in the following. EE-raised mice >PD400 had a contrast sensitivity of 14.6 ± 0.6 (corresponding to a contrast of 7%) before MD; this value increased by 86% to 27.2 ± 2.1 (4% contrast) after MD (n = 7; $p = 0.0005$, $p < 0.05$ for all the other spatial frequencies, *t*-test). Contrast sensitivity thresholds of EE-mice >PD700 increased by 33% from 8.9 ± 0.2 (11% contrast) on day 0 to 11.8 ± 0.6 (9% contrast) on day 7 (n = 8; $p = 0.0007$, $p < 0.01$ for all the other spatial frequencies, *t*-test). Late EE-mice showed a slight but not significant increase from 12.0 ± 1.3 (8% contrast) on day 0 to 14.7 ± 1.5 (7% contrast) on day 7 (n = 3; $p = 0.166$, $p > 0.05$ for all the other spatial frequencies, *t*-test).

4. Discussion

Plasticity is important for both regular brain functioning and experience- and learning-induced changes of neuronal circuitry, in particular for rehabilitation after brain injuries. Unfavorably, brain plasticity generally declines during aging. Our results provide clear evidence that raising mice in an EE with more animals housed together, and with access to labyrinths and running wheels, preserved a lifelong OD plasticity in V1. Notably, basic visual abilities of old SC- and EE-mice were not obviously different.

Most laboratory rodents such as mice and rats are raised in relatively small plastic cages, so-called SCs, in which about 3–5 animals are housed together. In these SC-mice, OD plasticity in V1 is maximal during the critical period, declines with age, and is usually absent beyond PD110 (Espinosa and Stryker, 2012; Levelt and Hübener, 2012). In contrast to SC-mice, raising mice in an EE increases brain plasticity and extensively modifies the molecular composition of the cortex compared with SC raising (for a review see Sale et al., 2014).

Although EE raising prolonged the sensitive phase for juvenile-like OD plasticity in mice until about PD200 (Greifzu et al., 2014), it was not clear whether OD plasticity persists into an even older age or disappears sometime during the lifespan of an EE mouse. Our new data show that, unlike SC-mice, EE-mice display a lifelong OD plasticity (oldest mouse tested: PD809). Additionally, the preserved OD shift after 7 days of MD was mediated by an increase in open eye responses in V1 of all EE-mice older than PD400. This is particularly interesting because OD shifts after 7 days of MD in EE-mice up to PD200 were mediated by reductions in deprived eye responses in V1 (Greifzu et al., 2014). Such reductions in deprived eye responses (juvenile OD plasticity) are a hallmark of juvenile-like OD plasticity

Table 1
Contrast sensitivity values measured by optomotry

Spatial frequency (cyc/deg)	Contrast sensitivity		
	EE >PD400	EE >PD700	Late EE >PD800
Day 0			
0.031	3.7 ± 0.05	3.7 ± 0.05	4.0 ± 0.13
0.064	14.6 ± 0.64	8.9 ± 0.22	12.0 ± 1.33
0.092	12.9 ± 0.48	8.2 ± 0.24	10.7 ± 1.15
0.103	12.0 ± 0.44	7.7 ± 0.19	10.3 ± 1.22
0.192	6.7 ± 0.32	6.8 ± 0.18	8.0 ± 0.49
0.272	3.6 ± 0.06	3.6 ± 0.07	3.9 ± 0.12
Day 7			
0.031	6.2 ± 0.65	4.9 ± 0.23	5.1 ± 0.41
0.064	27.2 ± 2.08	11.8 ± 0.60	14.7 ± 1.55
0.092	24.4 ± 1.82	11.3 ± 0.62	13.6 ± 1.27
0.103	22.7 ±1.53	10.8 ± 0.64	12.6 ± 1.07
0.192	15.1 ± 2.33	9.7 ± 0.70	9.9 ± 0.58
0.272	5.9 ± 0.70	4.7 ± 0.24	4.7 ± 0.24

Values before (day 0) and after (day 7) MD for mice raised in EE (>PD400 and >PD700) and transferred from SC to EE at PD110 (late EE, >PD800).
Key: EE, enriched environment; MD, monocular deprivation; PD, postnatal day; SC, standard cages.

(Levelt and Hübener, 2012) and are usually observed in SC-raised mice up to PD40, after just 4 days of MD (Frenkel and Bear, 2004; Hofer et al., 2006; Sato and Stryker, 2008). In contrast, in 2–3-month-old SC-mice, 7 days of MD are needed to induce OD plasticity and this plasticity is primarily mediated by increases in open eye responses in V1 (adult OD plasticity; Hofer et al., 2006; Sato and Stryker, 2008), like what we have observed in >PD400 EE-mice. Thus, the mechanism mediating OD plasticity of EE-mice is age-dependent, and the new data show that a switch from the juvenile (decrease in deprived eye responses in V1) to the adult form of OD plasticity (increase in open eye response) occurred sometime between PD200 and PD400 in EE-mice. This indicates that (1) EE-raising prolonged the sensitive phase for juvenile-like OD plasticity into late adulthood (at least until PD200) compared with SC-raising, and that (2) the adult form of OD plasticity started much later in EE compared to SC-mice (at around PD400).

EE-housing is also able to restore already lost plasticity. Several studies have shown that EE re-enabled OD plasticity in V1 of PD60-70 rats (Baroncelli et al., 2010, 2012) and in rats up to 23 months (Scali et al., 2012). Similarly, mice transferred from SC to EE cages beyond PD110 regained OD plasticity after 7 days of MD up to PD320 (Greifzu et al., 2014). Here, we show that this late EE preserved plasticity until PD922 (oldest animal tested). Thus, mice can display OD plasticity after MD until an age of at least 2.5 years, if they have the chance to experience enriched housing conditions from at least PD110.

EE-housing provides a multitude of stimuli compared with SC-rearing, raising the question whether all components are needed to enhance plasticity. Indeed physical exercise was already sufficient to enable recovery from amblyopia after long-term MD (Baroncelli et al., 2012) and to prolong and restore OD plasticity (Kalogeraki et al., 2014). Moreover, increased visual stimulation alone also enhanced amblyopia recovery and OD plasticity (Baroncelli et al., 2012; Matthies et al., 2013). Importantly, the plasticity-promoting effect of EE can be transmitted to future offspring: defective long-term potentiation (LTP) normally associated with a particular knock-out mouse line was not only masked in short-term enriched mice but also in their non-enriched offspring (Arai et al., 2009). These data underline the critical influence of the housing conditions on experimental animals and the outcome of plasticity experiments. Therefore, details of housing conditions, such as cage sizes, number of animals, whether animals had access to running wheels, toys, tunnels, and so forth should be provided in the methods section of all studies.

Furthermore, the Arai et al. (2009) study shows that the defective LTP-phenotype was only present when the knock-out mice were housed in an SC; supplying genetically identical mice with just 2 weeks of EE-experience in their youth prevented the defective LTP-phenotype (i.e., short-term EE-mice displayed normal LTP). Likewise, one could argue that OD plasticity might decline as early as it does in SC-raised mice because their environment is more deprived than for EE-mice. This interpretation suggests to cautiously discuss the importance of interventions promoting OD plasticity in the visual cortex of SC-raised adult rodents (Hübener and Bonhoeffer, 2014).

Although EE-raising clearly promotes visual cortical plasticity in mice, it was not yet known whether it also improves or changes visual performance. In fact, there is also a debate in the field whether enriched raising conditions affect sensory performance and/or interindividual variability. The present data indicate that this is rather unlikely because basic visual abilities were not different between old SC- and EE-mice: we did neither observe significant differences in visual acuity and orientation discrimination measured with the visual water task (Prusky and Douglas, 2004; Prusky et al., 2000b) nor in the visual parameters measured with the optomotor setup. The spatial frequency and contrast thresholds of the optomotor reflex of the old SC-mice were also similar to previously published data of SC-mice: Our mice reached values of 0.36 cyc/deg at PD690 which are comparable with 0.33 cyc/deg of the 24-month-old SC-mice (about PD730) of a previous study (Lehmann et al., 2012). Likewise, the visual acuity values measured with the visual water task were also similar to previously published data for similarly aged SC-mice (both C57BL/6J mice): our SC-mice had a mean visual acuity of 0.51 cyc/deg at PD690 compared with 0.52 cyc/deg at 24 months (about PD730; Lehmann et al., 2012). Summarizing, basic visual performance was not different between old EE- and SC-mice. This seems to be different at an earlier age: previous studies showed that the progressive increase of visual acuity that occurs during early postnatal life is accelerated by EE-housing in both mice (Cancedda et al., 2004; Prusky et al., 2000a) and rats (Landi et al., 2007b). The earlier acuity increase is most likely caused by an accelerated retinal development and an earlier eye opening in EE-mice (Cancedda et al., 2004; Landi et al., 2007a, 2007b, 2009; Sale et al., 2004, 2007a). Concerning the experience-enabled improvement of the spatial frequency threshold of the optomotor reflex of the open eye after MD, values of our EE-mice >PD700 were slightly but not significantly higher than in similarly aged SC-mice of a previous study (Lehmann et al., 2012).

Moreover, there were also neither differences between SC- and EE-mice in orientation discrimination abilities nor in learning time for the visual water task. Orientation discrimination values were 24° for SC-mice and 18° for EE-mice with an average age of about 700 days. Although there are no orientation discrimination values of comparably old mice in the literature, the perceptual thresholds of our old PD700 mice were nevertheless in the range of values reported for younger adult mice: PD100 SC-mice had a value of 11°, measured with the same method (Pielecka-Fortuna et al., 2014). Other behavioral tests revealed orientation discrimination thresholds of 10°–20° (Andermann et al., 2010; Reuter, 1987). Thus, although orientation discrimination abilities might slightly decrease with age, values of our old SC- and EE-mice (PD700) were still within the range of values reported for much younger adult SC-mice (≤PD100).

Our results, thus, indicate that visual acuity and other visual parameters are not higher in EE compared with SC-mice, and any initial difference disappears with age. There is, however, evidence that restrictions in visual experience, such as raising mice in SCs

with opaque walls, can decrease visual acuity (Prusky et al., 2000a). Whether extended training on visual tasks would enhance acuity remains to be determined.

Finally, EE-housing did not increase the variability of the data. We observed a similar variance in both SC- and EE-mice, and a similar increase of the interindividual variability of the values with age as described before for aging SC-mice (Lehmann et al., 2012). Summarizing, EE-housing had no obvious effect on basic visual abilities of the mice nor did it increase interindividual variability. However, there was a strong plasticity-promoting effect, emphasizing that individual sensory response properties (visual abilities vs. OD plasticity) can be mediated by different circuitry and molecular mechanisms (Fagiolini et al., 2003).

Taken together, our results show that enriched housing conditions allowed lifelong OD plasticity in mouse V1 by prolonging the sensitive phases for both juvenile-like and adult OD plasticity compared to SC-raised mice. However, EE-housing did not obviously affect basic visual abilities or their variance. This promotes an enriched surrounding as a powerful possibility to enhance brain plasticity before, during, and while aging.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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